# LRH-1 mitigates intestinal inflammatory disease by maintaining epithelial homeostasis and cell survival.

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**Public Summary:**

**Scientific Abstract:**

Epithelial dysfunction and crypt destruction are defining features of inflammatory bowel disease (IBD). However, current IBD therapies targeting epithelial dysfunction are lacking. The nuclear receptor LRH-1 (NR5A2) is expressed in intestinal epithelium and thought to contribute to epithelial renewal. Here we show that LRH-1 maintains intestinal epithelial health and protects against inflammatory damage. Knocking out LRH-1 in murine intestinal organoids reduces Notch signaling, increases crypt cell death, distorts the cellular composition of the epithelium, and weakens the epithelial barrier. Human LRH-1 (hLRH-1) rescues epithelial integrity and when overexpressed, mitigates inflammatory damage in murine and human intestinal organoids, including those derived from IBD patients. Finally, hLRH-1 greatly reduces disease severity in T-cell-mediated murine colitis. Together with the failure of a ligand-incompetent hLRH-1 mutant to protect against TNFalpha-damage, these findings provide compelling evidence that hLRH-1 mediates epithelial homeostasis and is an attractive target for intestinal disease.

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